(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/24769 A1

(51) International Patent Classification[7]: A61K 7/46, C12Q 1/18

(21) International Application Number: PCT/IB00/01389

(22) International Filing Date:
28 September 2000 (28.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/IB99/01618 4 October 1999 (04.10.1999) IB
PCT/IB99/01660 11 October 1999 (11.10.1999) IB

(71) Applicant *(for all designated States except US)*: **FIRMENICH SA** [CH/CH]; P. O. Box 239, 1, Route des Jeunes, CH-1211 Geneva 8 (CH).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **BRETLER, Gil** [CH/CH]; 23, Route du Bout-du-Monde, CH-1206 Geneva (CH).

(74) Agent: **SALVATERRA-GARCIA, Maria de Lurdes**; Firmenich SA, P. O. Box 239, 1, Route des Jeunes, CH-1211 Geneva 8 (CH).

(81) Designated States *(national)*: BR, JP, MX, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/24769 A1

(54) Title: ANTIMICROBIAL PERFUMING COMPOSITIONS

(57) Abstract: The present invention describes perfumes and perfuming compositions having an antimicrobial activity and containing effective amounts of certain perfuming ingredients which have an antimicrobial activity as evaluated by the Microbial Reduction Test.

ANTIMICROBIAL PERFUMING COMPOSITIONS

Technical Field and Prior Art

The present invention concerns the field of perfuming ingredients and compositions which have an antimicrobial effect. The application also describes a new test which is particularly adapted for determining the antimicrobial activity of perfuming ingredients.

In the perfume industry as well as in industries in which perfumes and perfuming compositions are used (as, for example, in companies which manufacture dish-washing liquids, all-purpose cleaners, shampoos or even cosmetic products), there is a great tendency towards the creation and use of perfuming compositions having an antimicrobial effect. This is due to the fact that there is an increasing consumer demand for products which have both an activity against bacteria and other microorganisms, and fulfil the consumer's expectations with regard to their lack of content in the currently used biocids such as Triclocarban and Triclosan.

It is known that certain perfuming ingredients of synthetic and natural origin do not only have a pleasant odor, but also have a more or less pronounced activity against microorganisms. However, this potential use of the perfuming ingredients has not been exploited in the past. The reason for this arises, to a great part, from the fact that there does not exist, according to our knowledge, a test allowing the evaluation in a quantitative, safe and reproducible way, of the true antimicrobial properties of perfuming ingredients.

The application EP-A-451 889 to Unilever gives a general survey of the various tests which are known to determine a certain antimicrobial activity of known perfuming compounds. The conclusion in the above application is that the methods disclosed are not reliable, e.g. because conflicting results have been obtained for a given ingredient against one and the same microorganism, or because results obtained for a certain microorganism cannot be transferred to another microorganism. As a solution to this problem, this prior art document describes a test called individual challenge test which is said to give reliable data on a compound's antimicrobial activity.

However, this known test does not provide quantitative results which permit a real evaluation of a compound's activity. Furthermore, the surfactants employed in the concentrations indicated (iso-octyl-phenoxypolyethoxy-ethanol and sodium dodecyl sulfate) do not solubilize the hydrophobic perfuming ingredients in the aqueous solution. The perfuming ingredient will be present to a greater part as a suspension of micelles. Therefore, they will not make proper contact with the inoculated bacteria, which are present in the aqueous phase. This creates an inherent error in the measurement and renders the procedure unreliable.

Description of the Invention

We have now developed a test which allows a quantitative and reliable evaluation of the antimicrobial activity of perfuming ingredients against a variety of different bacteria strains. This test is called "Microbial Reduction Test", and the test is particularly appropriate for perfuming ingredients.

In this specific " Microbial Reduction Test ", the perfuming ingredient to be evaluated is weighed into an aqueous test solution in a certain concentration (see below) and solubilized with an appropriate solvent which does not negatively affect the bacteria in the inoculum (to be added at a later stage). The appropriate solvents can be of a large variety of alcohols, for example, isopropanol, amyl alcohols and fusel oils. The preferred alcohol, however, is ethanol. We have surprisingly discovered that the addition of alcohols, and in particular of ethanol, makes it possible to obtain reliable and significant results on the antimicrobial activity of a perfuming ingredient, although it is known that ethanol itself has a certain bacteriostatic effect. However, we have surprisingly found that the use of the right amount of ethanol in the test according to the present invention has such a low effect on the bacteria that significant data of the antimicrobial activity of the test perfuming ingredient can be obtained. At the same time, the ethanol ensures a good solubilization of the hydrophobic perfuming ingredient in the aqueous phase which is used as a test medium.

The amount of ethanol to be used depends on the amount of perfuming ingredient present in the solution. The concentration of the latter will be between 250 and 1000 µg/ml, preferably between 300 and 800 µg/ml, with the most preferred

concentration ranging between 400 and 600 µg/ml. For the latter, it was found that ethanol concentrations in the test solution of between 5 and 20% by weight gave good results, the preferred concentration being around 15% by weight, based on the total weight of the test solution. These values are given with respect to the final aqueous solution containing the perfume, the ethanol and the inoculum.

When the perfuming ingredient is then solubilized in the test solution, at the above-identified concentrations, the solution is inoculated with the respective test bacterium to provide a final concentration of bacteria of 10^7 colony forming units (CFU)/ml.

The bacteria used were the following :

- *Escherichia coli*, ATCC 10536 (origin : American Type Culture Collection, Rockville, Md.)
- *Pseudomonas aeruginosa*, CNCN A22 (origin : Institut Pasteur, Paris)
- *Staphylococcus aureus*, ATCC 9144 (origin : Oxford Assay)
- *Enterococcus hirae*, ATCC 10541 (origin : FDA, USA).

After a contact time of between 2 and 10 min, preferably about 5 min at about 20°C, the aqueous test solution is then diluted with saline water to a concentration of about 10^3 CFU/ml. At this high dilution, the action of the perfuming ingredient on the bacteria is negligible. A volume corresponding to a theoretical maximum of 10^2 CFU's is then removed, spread on a culture medium, incubated and the number of colonies is counted. In practice, the test will in general be carried out by adding 0.1 ml test sample (containing 10^7 CFU's), to 9.9 ml of saline water and repeating the dilution with the solution obtained, until the desired concentration of about 10^3 CFU/ml was reached. From this solution, a 0.1 ml sample was spread on a casein-peptone dextrose yeast agar plate. The bacteria were then grown under appropriate conditions. We found that good results were obtained when the bacteria were grown overnight in an incubator at 37°C and a humidity of about 60-90%. The number of colonies were then evaluated, for example with a standard colony counter.

An antimicrobial activity rate for the respective product tested is then established by dividing the number of colony forming units for the bacteria exposed to the test product by the number of colony forming units counted in a reference or control

test in which the same bacterium has been submitted to the same testing sequence as above but without addition of a perfuming ingredient.

A perfuming ingredient is said to have successfully passed the test, i.e. is said to have an antimicrobial activity, when 100% of the respective bacteria have been eliminated.

According to the invention, the active molecules are defined as compounds which are active against 100% of the bacteria of two or three of the strains mentioned above. A non-limiting list of the compounds obeying the conditions of the present invention is given hereinbelow :

Decanal	Isoeugenal
10-Undecen-1-al	Nerol
Nonanal	Tetrahydrolinalool
4-Isopropylbenzaldehyde	Zestover [3]
4-Undecanolide	Intreleven aldehyde [4]
Citronellal	(2E,6Z)-2,6-nonadien-1-ol
Citronellol	γ-Dodecalactone
Cyclamen aldehyde	Floralozone [5]
Delphone [1]	Isobutylquinoleine
Dihydro eugenol	Lilial ® [6]
8-p-Menthanol	Mayol ® [7]
Dimetol [2]	Phenylhexanol
Geraniol	9-Decen-1-ol
3-(1,3-Benzodioxal-5-yl)-2-methylpropanal	

1) 2-Pentyl-1-cyclopentanone ; origin : Firmenich SA, Geneva, Switzerland

2) 2,6-Dimethyl-2-heptanol ; origin : Givaudan-Roure SA, Vernier, Switzerland

3) 2,4-Dimethyl-1-carbaldehyde : origin : Firmenich SA, Geneva, Switzerland

4) origin : International Flavors & Fragrances, USA

5) mixture of 3-(4-ethylphenyl)-2,2-dimethylpropanal + 3-(2-ethylphenyl)-2,2-dimethylpropanal : origin : International Flavors & Fragrances, USA

6) origin : Givaudan-Roure SA,Vernier, Switzerland

7) cis-7-p-menthanol ; origin : Firmenich SA, Geneva, Switzerland

Therefore, in the context of the present invention, an active molecule is defined as a compound having an antimicrobial activity as tested by the Microbial Reduction Test when it falls under the list given here-above. The use of these compounds as antimicrobial agents is an object of the present invention.

Another object of the present invention are compositions having an antimicrobial action and containing an effective amount of active molecules as defined above. We have found that, in order to be effective, such compositions should contain at least about 30% by weight, of the above-defined active molecules, with respect to the total weight of the composition. The preferred compositions are those which contain about 50% by weight of active molecules, with respect to the total weight of the composition.

Another object of the invention consists of a perfuming composition or a perfumed product containing an antimicrobial composition as defined above.

It is hence possible to prepare perfumes and colognes having an antimicrobial activity, by using a composition comprising active molecules according to the present invention, thus providing antimicrobial perfuming compositions. The antimicrobial perfuming compositions as defined above can advantageously be used to perfume certain products, in particular consumer products in the field of household and body care.

As it will appear from the examples below, these products, thanks to the presence of the antimicrobial compositions incorporated therein, acquire an antimicrobial activity themselves.

The activity of the final products will of course depend on the amount of perfuming composition present. Non-limiting examples for this type of application include soaps, bath and shower gels, shampoos, deodorants and antiperspirants, cosmetic compositions, air-fresheners, liquid and solid detergents for the treatment of textiles, fabric softeners and all-purpose cleaners for household and also industrial use.

In these applications, the antimicrobial compositions can be used alone or in admixture with other perfuming ingredients, solvents or adjuvants of current use in

perfumery. The nature and the variety of these coingredients do not require a more detailed description here, which, moreover, would not be exhaustive, and the person skilled in the art will be able to choose the latter through its general knowledge and as a function of the nature of the product to be perfumed and of the desired olfactive effect. These perfuming ingredients belong to chemical classes as varied as alcohols, aldehydes, ketones, esters, ethers, acetates, nitriles, terpene hydrocarbons, sulfur- and nitrogen-containing heterocyclic compounds, as well as essential oils of natural or synthetic origin. A large number of these ingredients is moreover listed in reference textbooks such as the book of S. Arctander, Perfume and Flavor Chemicals, 1969, Montclair, New Jersey, USA, or its more recent versions, or in other works of similar nature.

The invention will now be illustrated in greater detail in the following examples.

Embodiments of the Invention

Example 1

An antimicrobial composition was prepared with the following ingredients :

Ingredients	Parts by weight
Benzyl acetate	500
Hexylcinnamic aldehyde	1000
X (2E,6Z)-2,6-nonadien-1-ol*	5
X Citronellol	500
Coumarine	300
X γ-Dodecalactone	50
Lorysia ® 1)	1000
Heliotropine	200
X Isobutylquinoleine	50
X Lilial ®	2500
X Mayol ®	1000

Phenethylol	400
[X] Phenylhexanol	1500
Polysantol ®	500
Total	9505

* in dipropylene glycol

X = active compound according to the present invention

1) 4-(1,1-dimethylethyl)-1-cyclohexyl acetate ; origin : Firmenich SA, Geneva, Switzerland

The composition thus prepared showed an antimicrobial activity of 100% against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, as measured by the test according to the present invention.

Example 2

A perfuming composition was prepared by using the following ingredients :

Ingredients	Parts by weight
Benzyl acetate	500
Linalyl acetate	500
[X] Citronellol	300
[X] Cyclamen aldehyde	100
[X] γ-Dodecalactone	20
[X] Geraniol	200
Habanolide ® [1]	500
[X] Lilial ®	1000
[X] Mayol ®	300
Phenethylol	800
[X] Phenylhexanol	500

Benzyl salicylate	800
Terpineol	1000
Total	6520

x = active compound according to the present invention

1) mixture of pentadec-11-en-15-olide and pentadec-12-en-15-olide ; origin : Firmenich SA, Geneva, Switzerland

The composition thus prepared showed an antimicrobial activity of 100% against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, as measured by the test according to the present invention.

Example 3

There was prepared a perfuming composition using the following ingredients :

Ingredients	Parts by weight
x Nonanal	10
Hexylcinnamic aldehyde	800
x Intreleven aldehyde	10
x 4-Undecanolide	10
x Citronellol	1500
x Geraniol	1000
Habanolide ® 1)	800
Iralia ® Total 2)	200
Isopentyrate 3)	400
Dorisyl 1)	800
Lyral ® 4)	500
x Phenylhexanol	1000
x Tetrahydrolinalool	1500
Total	8530

x = active compound according to the present invention

1) see Example 2

2) methylionone mixture ; origin : Firmenich SA, Geneva, Switzerland

3) 1,3-dimethyl-3-butenyl isobutyrate ; origin : Firmenich SA, Geneva, Switzerland

4) mixture of 4- and 3-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carbaldehyde ; origin : International Flavors & Fragrances, USA

The composition thus prepared showed an antimicrobial activity of 100% against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, as measured by the test according to the present invention.

Example 4

Activity of antimicrobial perfuming compositions in a fabric softener

The *in vitro* Bacterial Contact Time (BCT) test provides a measure of the efficacy with which a product solution, at a certain concentration, will kill a given type of bacteria in the solution. This test is described in the international patent application WO 98/16194, the content of which is here-included by reference.

General method :

Three different antimicrobial compositions of the invention containing different percentages of active compounds formulated at 1%, were tested in a fabric softener base prepared from the following ingredients :

Ingredients	Parts by weight
Stepantex® VS90 [1)]	16.5
$CaCl_2$ (10% aqueous solution)	0.2
Dye (1% aqueous solution)	0.3
Water	82.0
Total	99.0

1) origin : Stepan, France

The bacteria used in this study were *Escherichia coli* ATCC 10536 (gram -) (origin : American Type Culture Collection, Rockville, Md).

The test organisms were grown in Tryptone Soya Broth (TSB) at 37° (OD_{600} = 1.0). After a 5 times dilution of the initial inoculum (OD_{600} = 0.2), 100 µl of bacteria were mixed with 100 µl of the sample softener. The bacteria kill was measured by sampling the bacteria/softener mix at short time intervals (respectively 30, 60, 90, 120, 180, 155 and 300 s) ; and then stopping the kill reaction by a dilution in TSB. When the reaction time was reached, 5µl of the preparation were diluted into 500µl and 5µl of this last preparation were diluted again into 50 volumes TSB. 50µl of the latter dilution were then plated on a Tryptone Soya Agent (TSA) plate and incubated overnight at 37°. The average colony number was estimated with a Countermat Flash (IUL Instruments).

Table 1 below reports the time (in s) required to achieved at least 99% kill, for respectively the unperfumed fabric softener base and the same base perfumed at 1% with 3 different antibacterial compositions of the invention, namely :

- antimicrobial composition 1 (AC 1) which is the composition described in Example 2 and which contains 37% of active compounds according to the invention ;
- antimicrobial composition 2 (AC 2) which is the composition described in Example 3 and which contains 59% of active compounds according to the invention ; and
- antimicrobial composition 3 (AC 3) which contains 100% of active compounds according to the invention and which was prepared by using the following ingredients :

Ingredients	Parts by weight
Nonanal	10
Intreleven aldehyde	10
4-Undecanolide	10
Citronellol	1500
Geraniol	1000
Phenylhexanol	1000
Tetrahydrolinalool	1500
Total	5030

Table 1 : *Bacterial Contact Test carried out respectively on a fabric softener base unperfumed and on the same base perfumed with 3 different compositions*

Composition tested	Percentage of active ingredients	Time for kill [s] 99%
Softener base (SB) unperfumed	0	300
SB perfumed with AC 1	37	255
SB perfumed with AC 2	59	90
SB perfumed with AC 3	100	30

It clearly appears from these results that the softener base comprising the antimicrobial compositions of the invention performed better than the base alone which required at least 300 s to reach a 99% kill. Composition of fabric softener and AC 3 (containing 100% active ingredients) also attained a 99.9% kill after a contact time of 90 s. Probability values for 99 and 99.9% kills were 0.1 and 0.01 respectively.

CLAIMS

1. Antimicrobial composition, characterised in that it contains an effective amount of one or more active compounds the antimicrobial activity of which is 100% when measured by the Microbial Reduction Test.

2. An antimicrobial composition according to claim 1, characterised in that the active compound is chosen from the group consisting of decanal, 10-undecen-1-al, nonanal, 4-isopropylbenzaldehyde, 4-undecanolide, citronellal, citronellol, cyclamen aldehyde, delphone, didydro eugenol, 8-p-menthanol, dimetol, geraniol, 3-(1,3-benzodioxal-5-yl)-2-methylpropanal, isoeugenal, nerol, tetrahydrolinalool, zestover, intreleven aldehyde, (2E,6Z)-2,6-nonadien-1-ol, γ-dodecalactone, floralozone, isobutylquinoleine, Lilial®, Mayol®, phenylhexanol, 9-decen-1-ol.

3. Antimicrobial composition according to claim 1 or 2, characterised in that it contains at least 30% by weight of active compounds.

4. Antimicrobial composition according to claim 1 or 2, characterised in that it contains at least 50% by weight of active compounds.

5. Perfuming composition or perfumed article containing an antimicrobial composition according to any one of claims 1 to 4.

6. A perfumed article according to claim 5, in the form of a soap, a bath or shower gel, a shampoo or other hair-care product, a deodorant or antiperspirant, a cosmetic preparation, an air-freshener, a liquid or solid detergent for the treatment of textiles, a fabric softener or an all-purpose cleaner for household or industrial use.

7. Use of a composition according to any one of claims 1 to 4, to impart an antimicrobial activity or to enhance the antimicrobial activity of an article for personal care or a functional product.

8. A method to evaluate the antimicrobial activity of a compound, characterised in that said method comprises :

- solubilizing in an aqueous medium in a concentration between 250 and 1000 µg/ml relative to the medium of the ingredient to be tested in the presence of an effective amount of solvent which is substantially non toxic for a subsequently added bacteria and which allows a complete solubilizing of said perfuming ingredient;
- adding an inoculum of the desired bacterium such that the final concentration in the medium will be 10^7 colony forming units/ml of the medium;
- diluting the medium so as to reduce the bacteria concentration to 10^3 colony forming units/ml of medium;
- spreading 10^2 bacteria onto an appropriate culture medium, counting the surviving colonies after incubation and comparing the value obtained with a control, containing no perfume.

9. The method according to claim 8, characterised in that the solvent is an alcohol.

10. The method according to claim 9, characterised in that the alcohol is ethanol.

11. The method according to any one of claims 8 to 10, characterised in that the ethanol concentration in the aqueous medium is between 5 and 20% by weight, preferably around 15% by weight, with respect to the total weight of the medium.

12. The method according to any one of claims 8 to 11, characterised in that the contact time is about 5 min.

13. The method according to any one of claims 8 to 12, characterised in that the concentration of perfuming ingredient in the aqueous medium is between 400 and 600 µg/ml.

14. The method according to any one of claims 8 to 13, characterised in that the bacteriae are selected from the group consisting of the species *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus hirae*.

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/IB 00/01389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/46 C12Q1/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOLZNER G.: "The examination of the effectiveness of body deodorant sprays" AEROSOL REPORT, vol. 25, 7 August 1986 (1986-08-07), pages 354-369, XP000929204 page 357, column 2 page 364, column 2, paragraphs 1-4 page 365, column 2, paragraphs 3,4 page 369, column 2, paragraph 3 ---	1-7
X	EP 0 451 889 A (UNILEVER PLC ;UNILEVER NV (NL)) 16 October 1991 (1991-10-16) cited in the application page 2, line 2-4,13,14,51-58 page 3, line 4-7,11-14,56-58 page 4, line 28-46 examples I-V,1-8 claims 1,5,10,13 --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	01/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bazzanini, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 00/01389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 5 420 104 A (HOLZNER GUENTER ET AL) 30 May 1995 (1995-05-30) column 1, line 50 -column 2, line 7 column 3, line 16-29,58-67 column 4, line 26-33 column 5, line 3-13,39-42 column 6, line 34-51 examples 1-9 claims 1,9,10,12-20	1,2,5-7
X	MORRIS J A ET AL: "ANTIMICROBIAL ACTIVITY OF AROMA CHEMICALS AND ESSENTIAL OILS" JOURNAL OF THE AMERICAN OIL CHEMISTS' SOCIETY,AMERICAN OIL CHEMISTS' SOCIETY. CHAMPAIGN,US, 1 May 1979 (1979-05-01), pages 595-603, XP000645444 ISSN: 0003-021X page 595, column 1, paragraph 2 page 595, column 2, paragraph 2 table 1 page 596, column 2, paragraph 2	1,2,5-7
X A	US 5 403 587 A (MCCUE KAREN A ET AL) 4 April 1995 (1995-04-04) column 1, line 56 -column 2, line 19,46-58 column 3, line 59 -column 4, line 3 column 6, line 12-16,24-61 table IV claims 1,3	1,5-7 8-14
X	WO 98 02044 A (TRANI MARINA ;ROMANO NICOLETTA (IT); BAKER KEITH HOMER (US); PROCT) 22 January 1998 (1998-01-22) page 2, line 5-12 page 11, line 5-37 page 12, line 8-11,22-27 page 15, line 22-36 examples I-XII claims 1,5	1,5-7

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7

Present claims 1-7 relate to a compound/product defined by reference to the following parameter:

P1: antimicrobial activity measured by the Microbial Reduction Test.

The use of these parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameter the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the products mentioned in the description at page 4, lines 11-17 and in claim 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/IB 00/01389

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